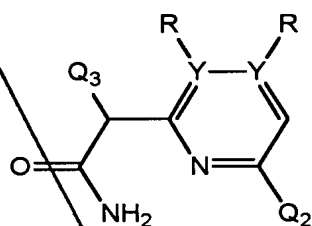


Cpd #	Structure	Cpd #	Structure
208		209	

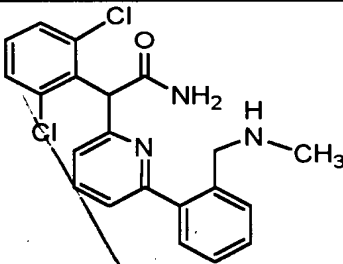
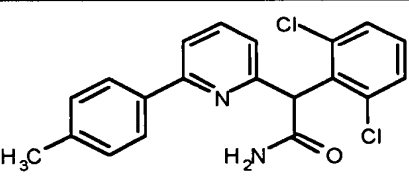
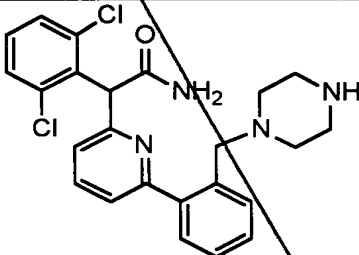
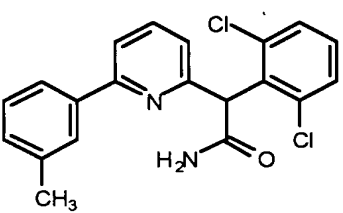
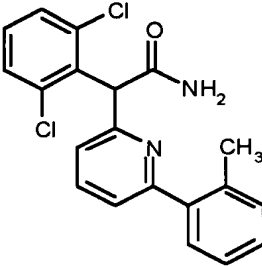
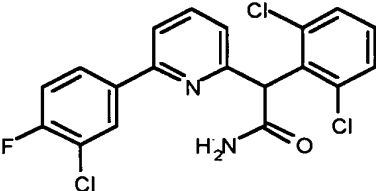
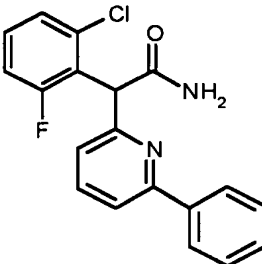
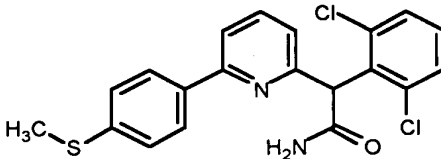
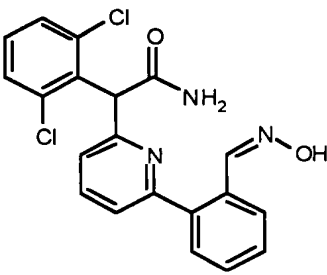
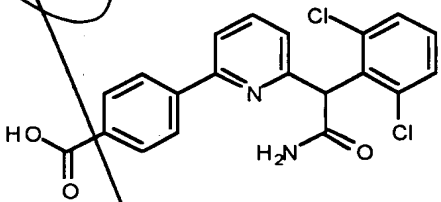
23. (Twice amended) The compound according to claim 39, wherein said compound is a compound of formula Ig:



and is selected from any one of the following compounds:

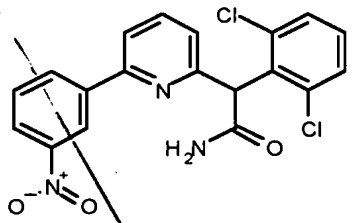
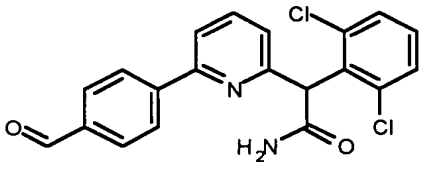
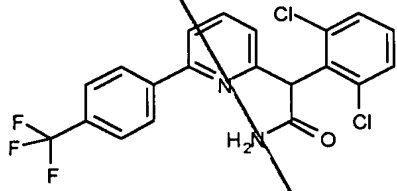
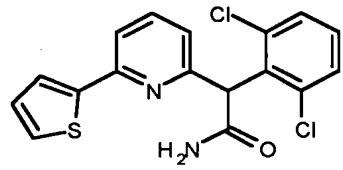
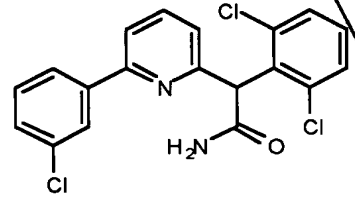
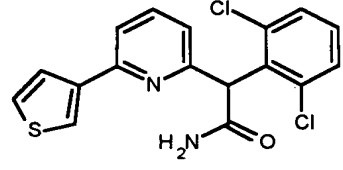
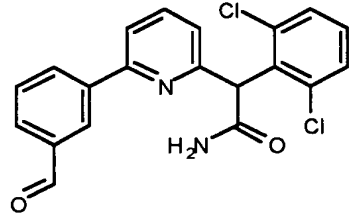
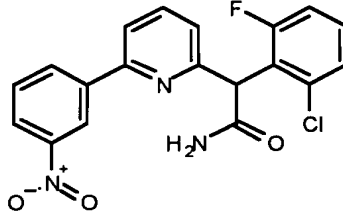
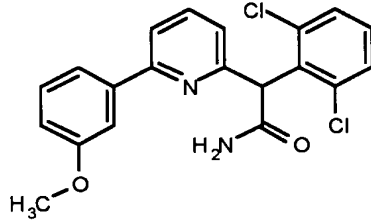
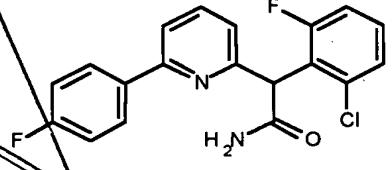
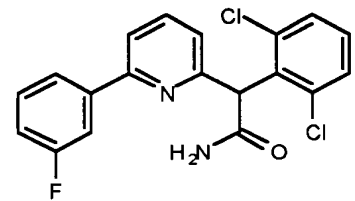
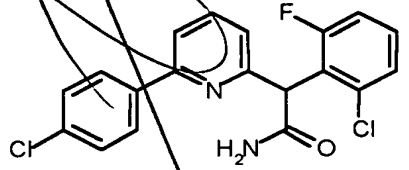
cpd #	Structure	cpd #	structure
302		310	

C3
cont

303		311	
304		312	
305		313	
306		314	
307		315	

C

Q3
Cont

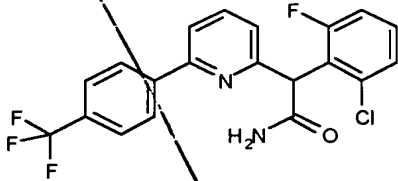
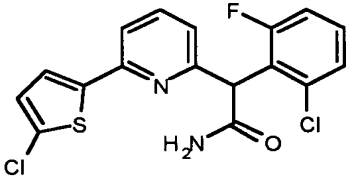
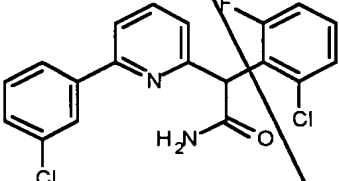
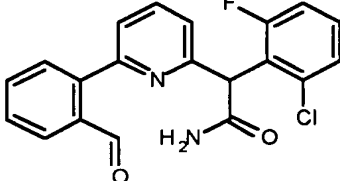
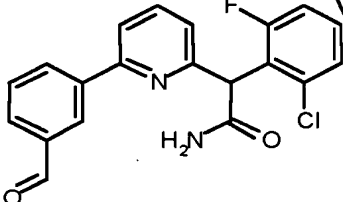
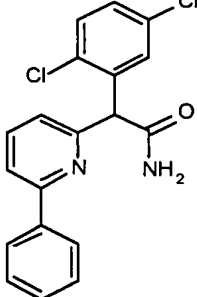
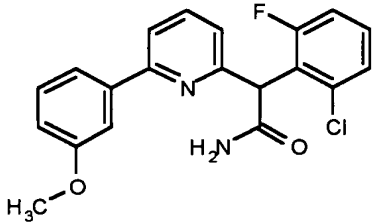
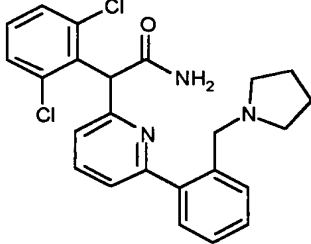
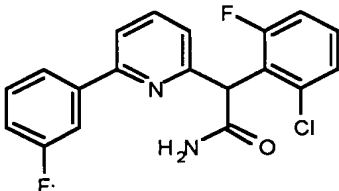
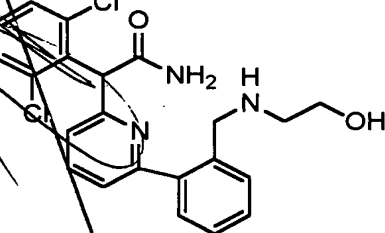
308		316	
319		317	
320		318	
321		328	
322		329	
323		330	

C3
Cont

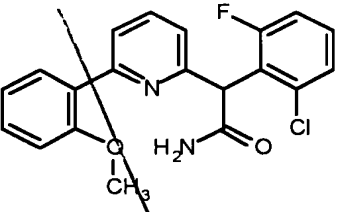
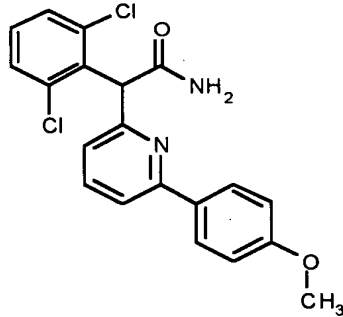
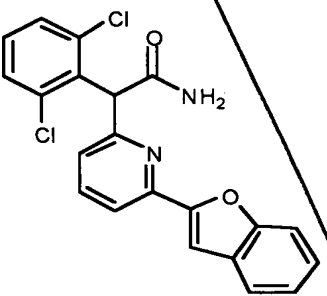
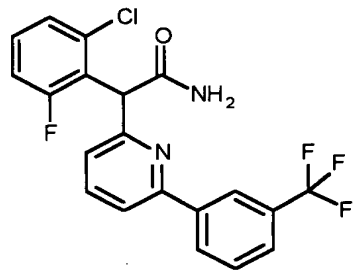
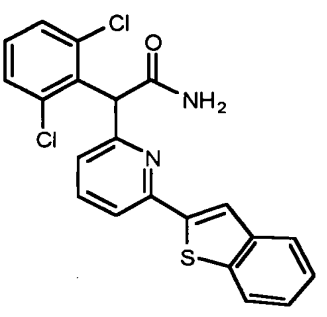
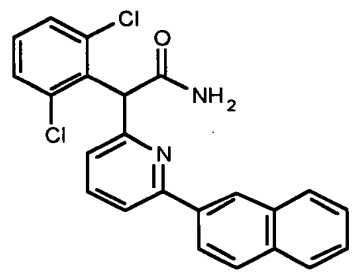
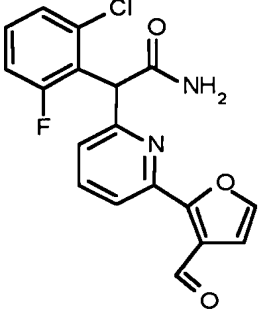
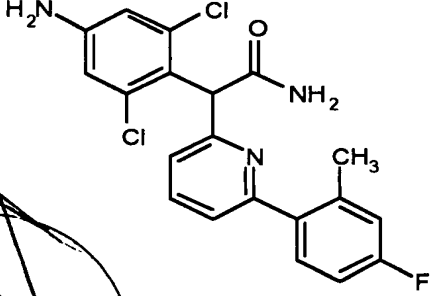
324		331	
325		332	
326		333	
327		334	
337		335	
338		336	
339		346	

C

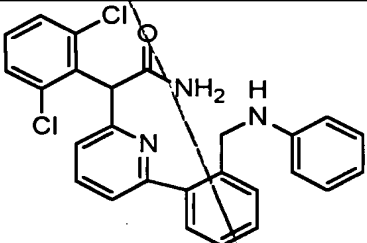
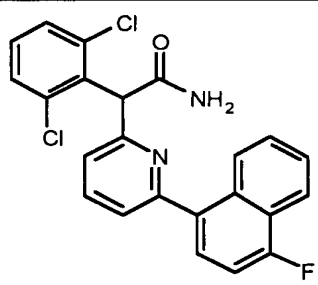
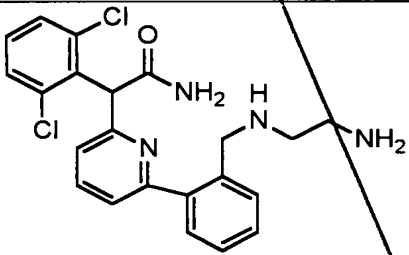
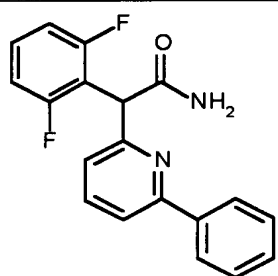
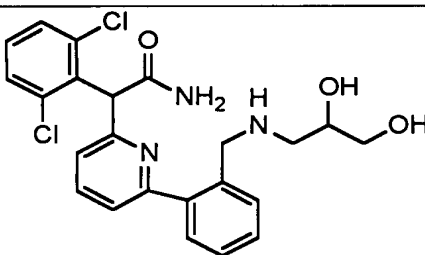
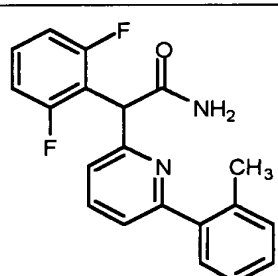
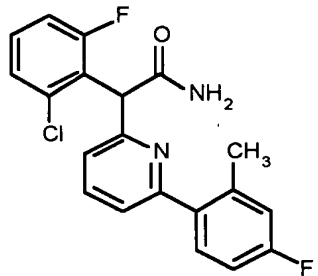
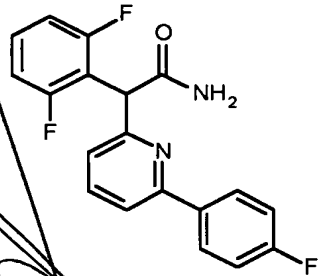
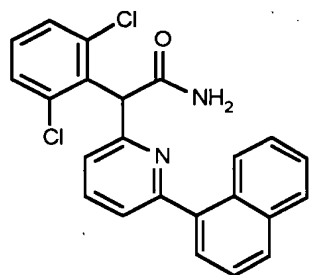
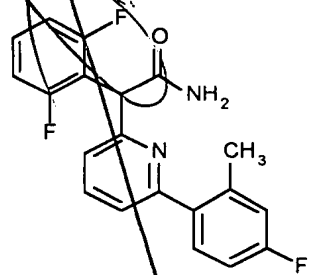
03
Cont

340		347	
341		348	
342		349	
343		350	
344		351	

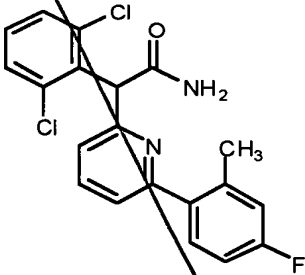
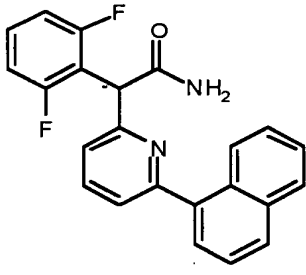
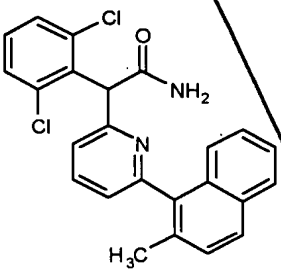
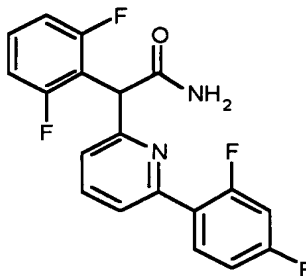
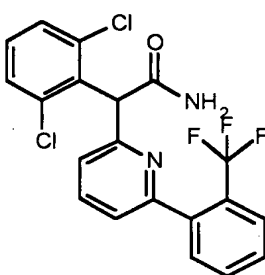
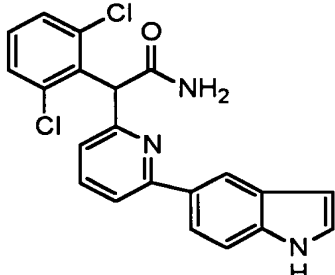
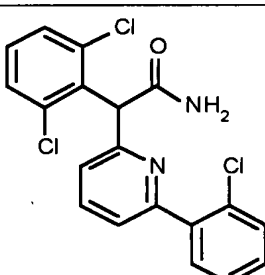
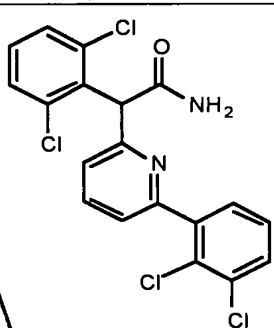
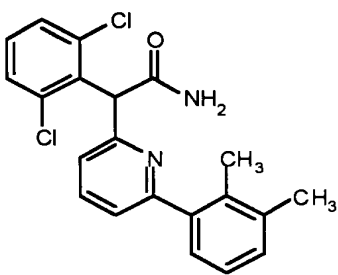
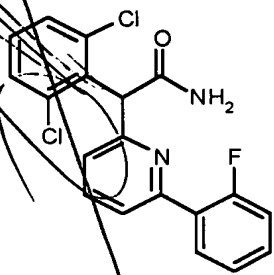
C₃
cont

345		352	
355		353	
356		354	
357		364	

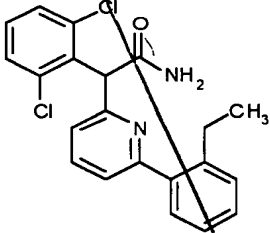
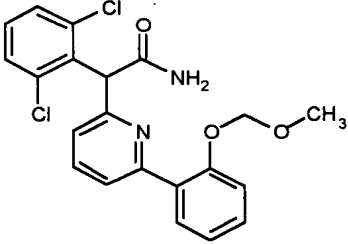
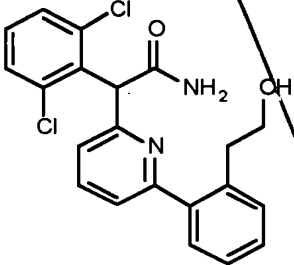
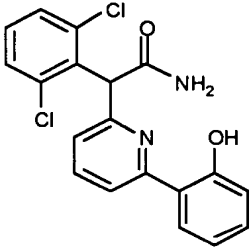
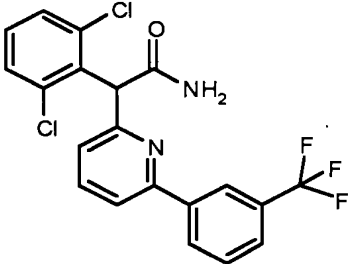
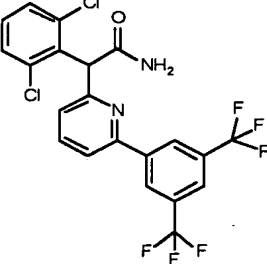
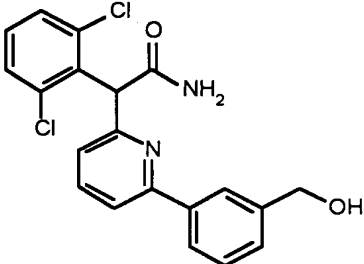
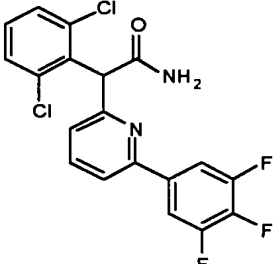
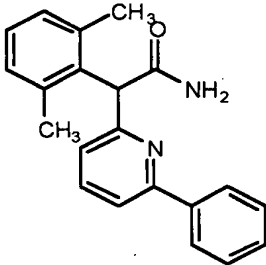
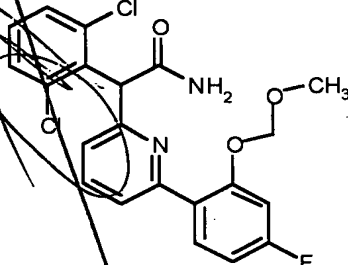
Q3
Cont

358		365	
359		366	
360		367	
361		368	
362		369	

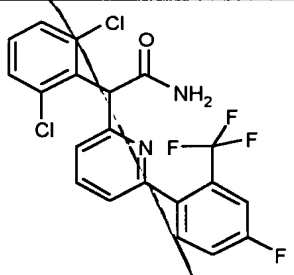
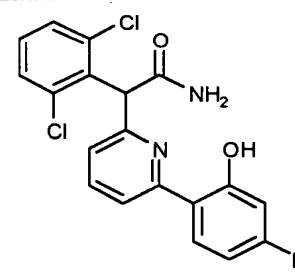
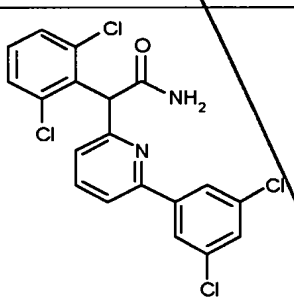
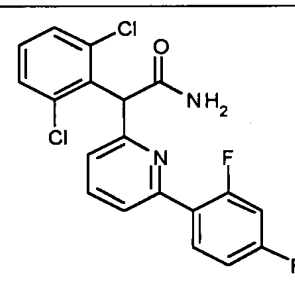
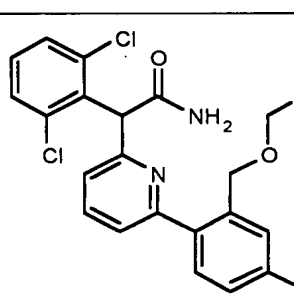
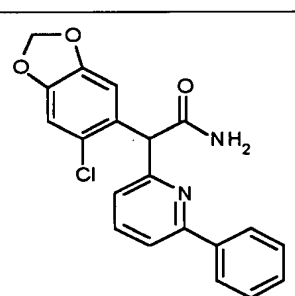
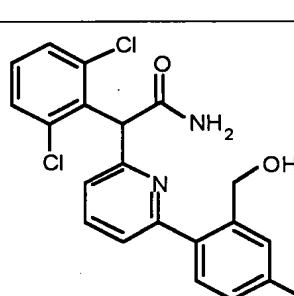
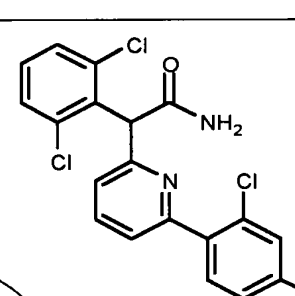
C3
Cont

363		370	
373		371	
374		372	
375		382	
376		383	

C₃
Cont

377		385	
378		386	
379		387	
380		388	
381		389	

C3
cont

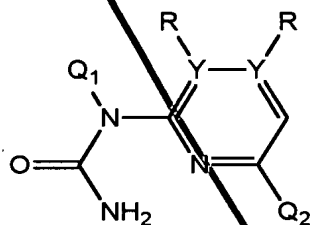
391		390	
392		396	
393		397	
394		398	

C

C3
cont

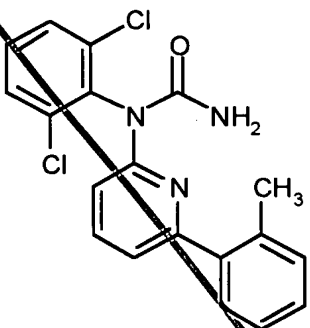
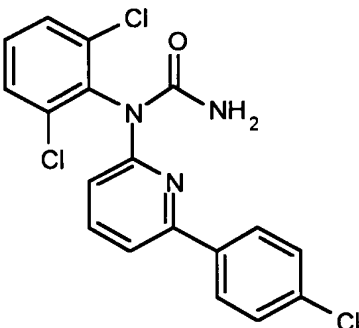
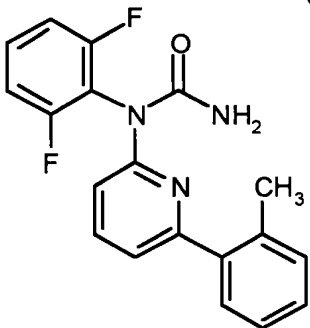
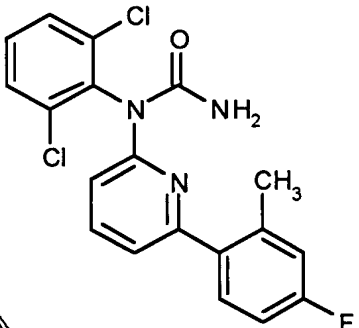
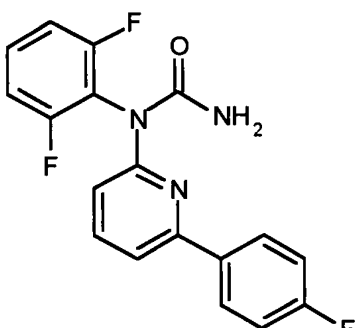
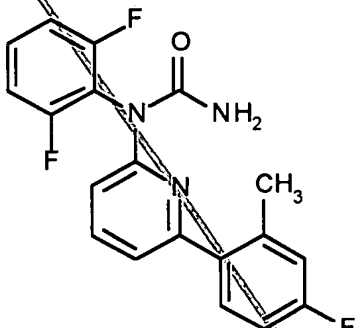
395		399	
		1361	

24. (Twice amended) The compound according to claim 38, wherein said compound is a compound of formula 1h:



and is selected from any one of the following compounds:

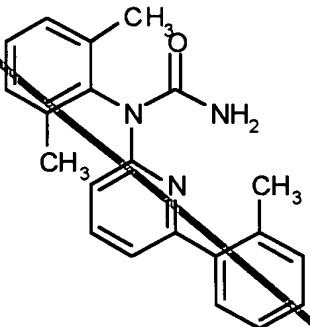
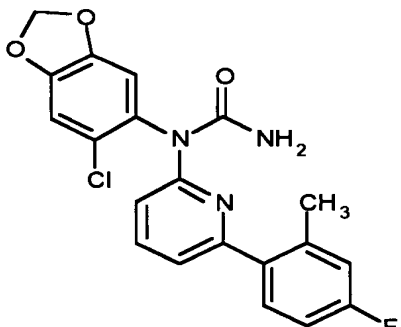
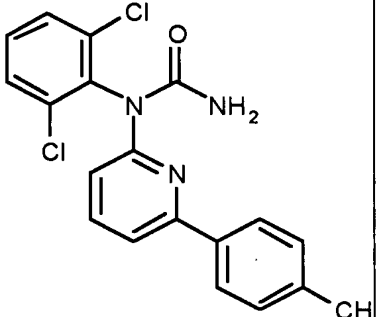
cpd #	structure	Cpd #	Structure
401		407	

Cpd #	structure	Cpd #	Structure
402		408	
403		409	
404		410	

E1
cont
C3
cont

C

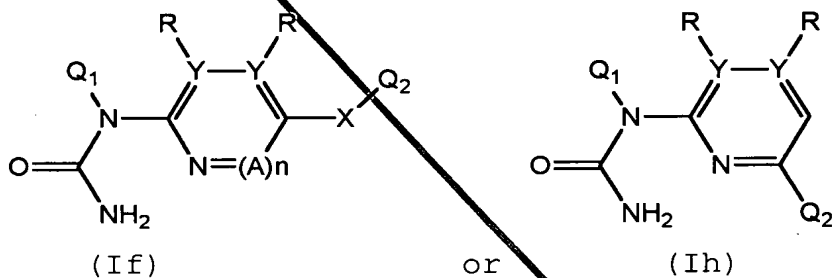
C3
cont
E1
cont

405		411	
406			

C4

23 ~~29~~ (Twice amended) The method according to claim ~~26~~ ²⁰, wherein said method is used to treat a destructive bone disorder selected from osteoarthritis, osteoporosis or multiple myeloma-related bone disorder.

38. (Twice Amended) A compound of the formula:



wherein:

each of Q₁ and Q₂ are independently selected from 5-6 membered aromatic carbocyclic or heterocyclic ring systems, or 8-10 membered bicyclic ring systems consisting of aromatic carbocyclic rings, aromatic heterocyclic rings or a combination of an aromatic carbocyclic ring and an aromatic heterocyclic ring; wherein:

E3 cont
C^s cont
Q₁ is substituted with 1 to 4 substituents, independently selected from halo; C₁-C₃ alkyl optionally substituted with NR'₂, OR', CO₂R' or CONR'₂; O-(C₁-C₃)-alkyl optionally substituted with NR'₂, OR', CO₂R' or CONR'₂; NR'₂; OCF₃; CF₃; NO₂; CO₂R'; CONHR'; SR'; S(O₂)N(R')₂; SCF₃; CN; N(R')C(O)R⁴; N(R')C(O)OR⁴; N(R')C(O)C(O)R⁴; N(R')S(O₂)R⁴; N(R')R⁴; N(R⁴)₂; OR⁴; OC(O)R⁴; OP(O)₃H₂; or N=CH-N(R')₂; and

Q₂ is optionally substituted with up to 4 substituents, independently selected from halo, CH=N-OH, or CH=O; C₁-C₃ straight or branched alkyl optionally substituted with NR'₂, OR', CO₂R', S(O₂)N(R')₂, N=CH-N(R')₂, R³, NH-CH₃, NHCH₂CH₂OH, NHCH₂OH(OH)CH₂OH, CH₂OCH₂OCH₃, NHCH₂CH₂NH₂, NH-phenyl, piperazinyl, pyrrolidinyl or CONR'₂; O-(C₁-C₃)-alkyl optionally substituted with NR'₂, OR', CO₂R', S(O₂)N(R')₂, N=CH-N(R')₂, R³, or CONR'₂; NR'₂; OCF₃; CF₃; NO₂; CO₂R'; CONHR'; R³; OR³; NHR³; SR³; C(O)R³; C(O)N(R')R³; C(O)OR³; SR'; S(O₂)N(R')₂; SCF₃; N=CH-N(R')₂; CH=N-OH; CH=O; or CN;

wherein R' is selected from hydrogen, (C₁-C₃)-alkyl; (C₂-C₃)-alkenyl or alkynyl; phenyl or phenyl substituted with 1 to 3 substituents independently selected from halo, methoxy, cyano, nitro, amino, hydroxy, methyl or ethyl;

R³ is selected from a 5-6 membered aromatic carbocyclic or heterocyclic ring system;

R⁴ is (C₁-C₄)-alkyl optionally substituted with N(R')₂, OR', CO₂R', CON(R')₂, or SO₂N(R²)₂; or a 5-6 membered carbocyclic or heterocyclic ring system optionally substituted with N(R')₂, OR', CO₂R', CON(R')₂, or SO₂N(R²)₂;

X is selected from -S-, -O-, -S(O₂)-, -S(O)-, -S(O₂)-, N(R²)-, -N(R²)-S(O₂)-, -N(R²)-C(O)O-, -O-C(O)-N(R²), -C(O)-, -C(O)O-, -O-C(O)-, -C(O)-N(R²)-, -N(R²)-C(O)-, -N(R²)-, -C(R²)₂-, -C(OR²)₂-, -CH(OH)-;

each R is independently selected from hydrogen, -R², -N(R²)₂, -OR², SR², -C(O)-N(R²)₂, -S(O₂)-N(R²)₂, or -C(O)-OR², wherein two adjacent R are optionally bound to one

C

C⁵
Cont
C³
cont

another and, together with each Y to which they are respectively bound, form a 4-8 membered carbocyclic or heterocyclic ring;

R² is selected from hydrogen, (C₁-C₃)-alkyl, or (C₁-C₃)-alkenyl; each optionally substituted with -N(R')₂, -OR', SR', -C(O)-N(R')₂, -S(O₂)-N(R')₂, -C(O)-OR', or R³;

Y is C;

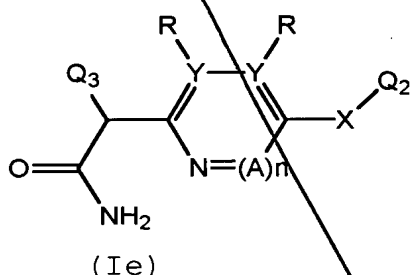
A is CR'; and

n is 1; wherein an aromatic heterocyclic ring system comprises 1-2 heteroatoms independently selected from N, O or S.

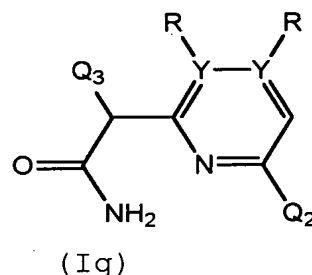
Please add the following claims 39-67:

C⁶

39. (Added) A compound of the formula:



or



wherein:

Q₃ is a 5-6 membered aromatic carbocyclic or heterocyclic ring system; or an 8-10 membered bicyclic ring system comprising aromatic carbocyclic rings, aromatic heterocyclic rings or a combination of an aromatic carbocyclic ring and an aromatic heterocyclic ring; wherein Q₃ is substituted with 1 to 4 substituents, each of which is independently selected from halo; C₁-C₃ alkyl optionally substituted with NR'₂, OR', CO₂R' or CONR'₂; O-(C₁-C₃)-alkyl optionally substituted with NR'₂, OR', CO₂R' or CONR'₂; NR'₂; OCF₃; CF₃; NO₂; CO₂R'; CONHR'; SR'; S(O₂)N(R')₂; SCF₃; CN; N(R')C(O)R⁴; N(R')C(O)OR⁴; N(R')C(O)C(O)R⁴; N(R')S(O₂)R⁴; N(R')R⁴; N(R⁴)₂; OR⁴; OC(O)R⁴; OP(O)₃H₂; or N=CH-N(R')₂;

Q₂ is selected from 5-6 membered aromatic

C

carbocyclic or heterocyclic ring systems, or 8-10 membered bicyclic ring systems consisting of aromatic carbocyclic rings, aromatic heterocyclic rings or a combination of an aromatic carbocyclic ring and an aromatic heterocyclic ring; wherein:

Q₂ is optionally substituted with up to 4 substituents, independently selected from halo, CH=N-OH, or CH=O; C₁-C₃ straight or branched alkyl optionally substituted with NR'₂, OR', CO₂R', S(O₂)N(R')₂, N=CH-N(R')₂, R³, NH-CH₃, NHCH₂CH₂OH, NHCH₂CH(OH)CH₂OH, CH₂OCH₂OCH₃, NHCH₂CH₂NH₂, NH-phenyl, piperazinyl, pyrrolidinyl or CONR'₂; O-(C₁-C₃)-alkyl optionally substituted with NR'₂, OR', CO₂R', S(O₂)N(R')₂, N=CH-N(R')₂, R³, or CONR'₂; NR'₂; OCF₃; CF₃; NO₂; CO₂R'; CONHR'; R³; OR³; NHR³; SR³; C(O)R³; C(O)N(R')R³; C(O)OR³; SR'; S(O₂)N(R')₂; SCF₃; N=CH-N(R')₂; CH=N-OH; CH=O; or CN;

wherein R' is selected from hydrogen, (C₁-C₃)-alkyl; (C₂-C₃)-alkenyl or alkynyl; phenyl or phenyl substituted with 1 to 3 substituents independently selected from halo, methoxy, cyano, nitro, amino, hydroxy, methyl or ethyl;

R³ is selected from a 5-6 membered aromatic carbocyclic or heterocyclic ring system;

R⁴ is (C₁-C₄)-alkyl optionally substituted with N(R')₂, OR', CO₂R', CON(R')₂, or SO₂N(R²)₂; or a 5-6 membered carbocyclic or heterocyclic ring system optionally substituted with N(R')₂, OR', CO₂R', CON(R')₂, or SO₂N(R²)₂;

X is selected from -S-, -O-, -S(O₂)-, -S(O)-, -S(O₂)-, N(R²)-, -N(R²)-S(O₂)-, -N(R²)-C(O)O-, -O-C(O)-N(R²), -C(O)-, -C(O)O-, -O-C(O)-, -C(O)-N(R²)-, -N(R²)-C(O)-, -N(R²)-, -C(R²)₂-, -C(OR²)₂-, -CH(OH)-;

each R is independently selected from hydrogen, -R², -N(R²)₂, -OR², SR², -C(O)-N(R²)₂, -S(O₂)-N(R²)₂, or -C(O)-OR², wherein two adjacent R are optionally bound to one another and, together with each carbon to which they are respectively bound, form a 4-8 membered carbocyclic or

heterocyclic ring;

R^2 is selected from hydrogen, (C_1-C_3) -alkyl, or (C_1-C_3) -alkenyl; each optionally substituted with $-N(R')_2$, $-OR'$, SR' , $-C(O)-N(R')_2$, $-S(O_2)-N(R')_2$, $-C(O)-OR'$, or R^3 ;

Y is C;

A is CR' ; and

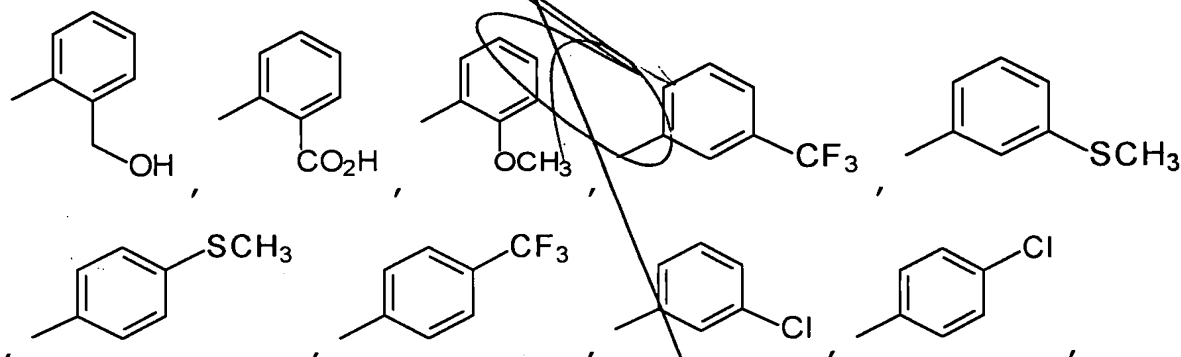
n is 1; wherein an aromatic heterocyclic ring system comprises 1-2 heteroatoms independently selected from N, O or S;

provided that for a compound of formula Ig, when Q_3 is 2,6-dichlorophenyl and both R substituents are H, then Q_2 is neither phenyl nor p-fluorophenyl; and

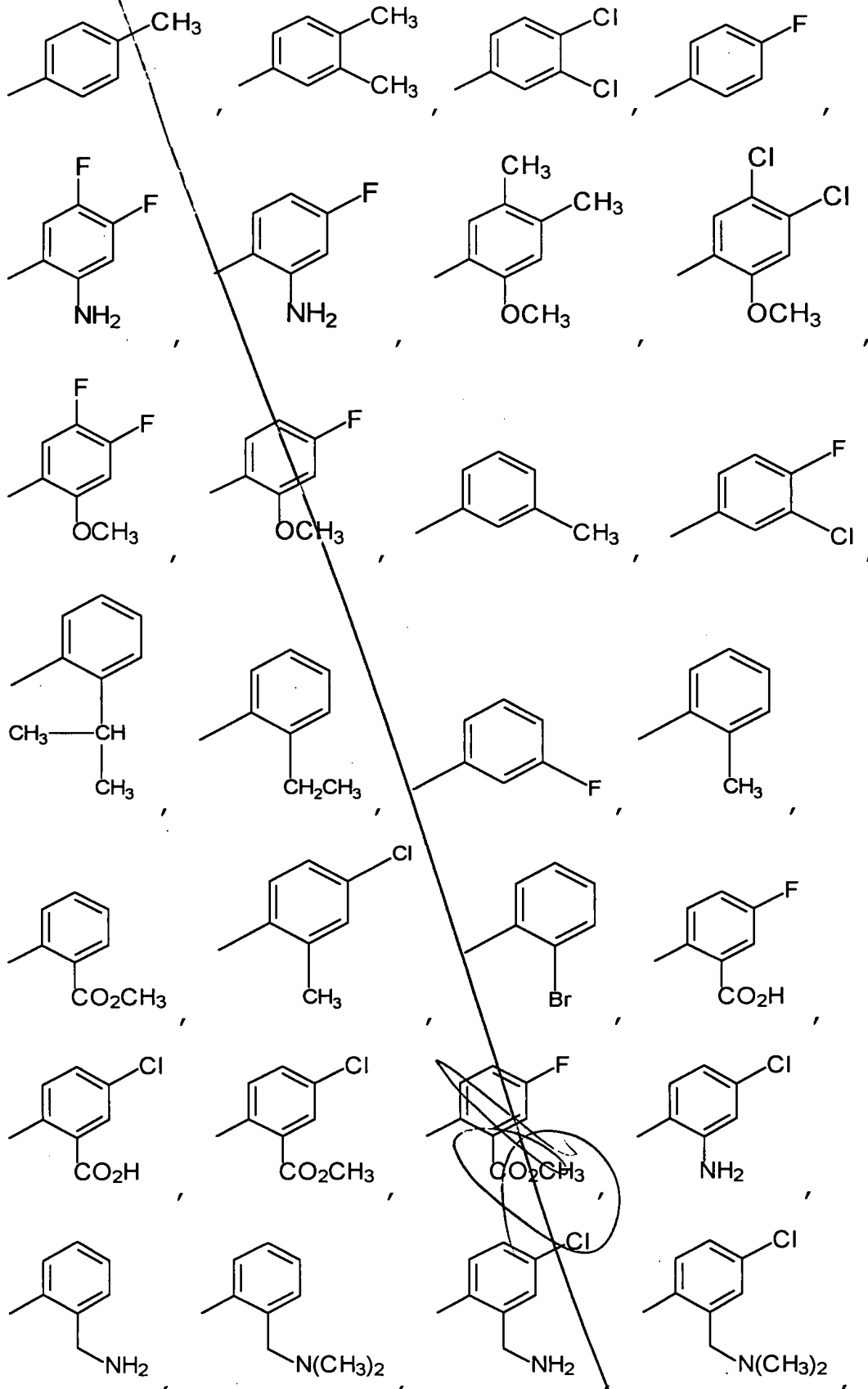
for a compound of formula Ie, when Q_3 is 2,6-dichlorophenyl, both R substituents are H, and X is S, then Q_2 is not phenyl.

40. (Added) The compound according to claim 39, wherein Q_2 is selected from phenyl or pyridyl and wherein Q_2 optionally contains up to 3 substituents, each of which is independently selected from chloro, fluoro, bromo, methyl, ethyl, isopropyl, $-OCH_3$, $-OH$, $-NH_2$, $-CF_3$, $-OCF_3$, $-SCH_3$, $-OCH_3$, $-C(O)OH$, $-C(O)OCH_3$, $-CH_2NH_2$, $-N(CH_3)_2$, $-CH_2$ -pyrrolidine and $-CH_2OH$.

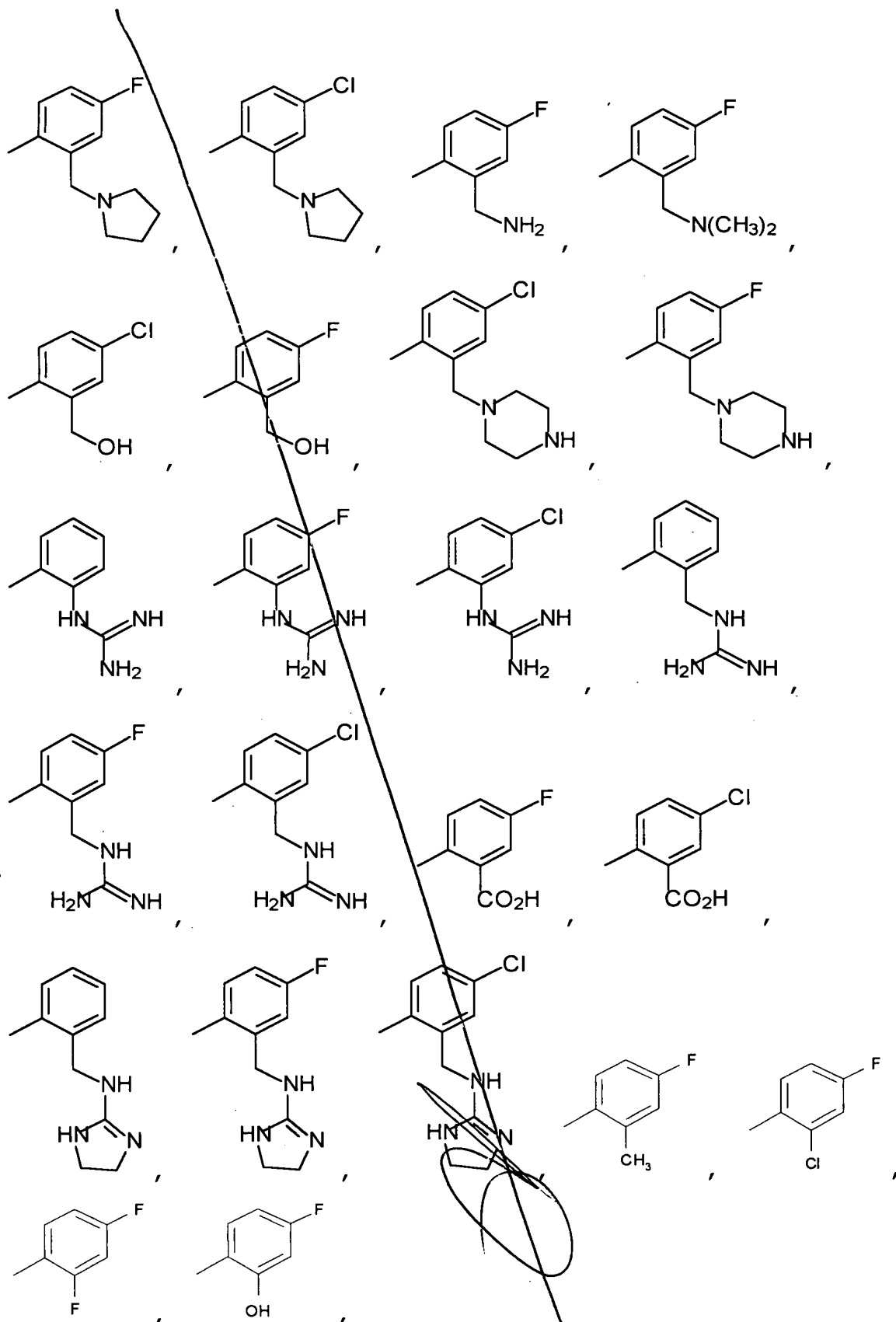
41. (Added) The compound according to claim 40, wherein, Q_2 is selected from:



26



C6



unsubstituted 2-pyridyl or unsubstituted phenyl.

C

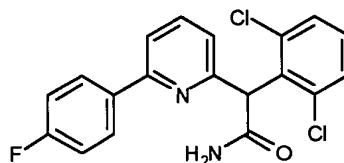
42. (Added) The compound according to claim 41, wherein Q₂ is selected from phenyl, 2-isopropylphenyl, 3,4-dimethylphenyl, 2-ethylphenyl, 3-fluorophenyl, 2-methylphenyl, 3-chloro-4-fluorophenyl, 3-chlorophenyl, 2-carbomethoxyphenyl, 2-carboxyphenyl, 2-methyl-4-chlorophenyl, 2-bromophenyl, 2-pyridyl, 2-methylenedihydroxyphenyl, 4-fluorophenyl, 2-methyl-4-fluorophenyl, 2-chloro-4-fluorophenyl, 2,4-difluorophenyl, 2-hydroxy-4-fluorophenyl or 2-methylenedihydroxy-4-fluorophenyl.

C6
43. (Added) The compound according to claim 39, wherein X is selected from -S-, -O-, -S(O₂)-, -S(O)-, -NR²-, -C(R²)₂- or -C(O)-.

44. (Added) The compound according to claim 42, wherein X is S.

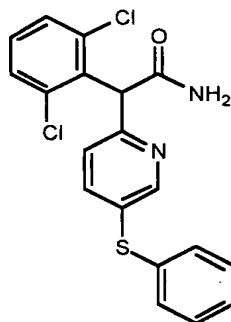
45. (Added) The compound according to claim 39, wherein each R attached to Y is independently selected from hydrogen or methyl.

13 46. (Added) A compound of the formula



111260
14 47. (Added) A compound of the formula

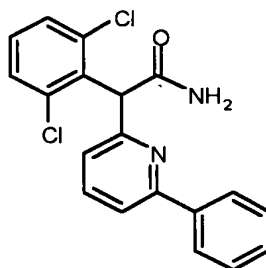
T, 1270



15

48. (Added) A compound of the formula

T, 1271
C6



49. (Added) A pharmaceutical composition comprising an amount of a compound according to claim 39 effective to inhibit p38, and a pharmaceutically acceptable carrier.

50. (Added) A method of treating inflammatory diseases, autoimmune diseases, viral diseases, destructive bone disorders, proliferative disorders, infectious diseases, neurodegenerative diseases, reperfusion/ischemia in stroke, myocardial ischemia, renal ischemia, heart attacks, angiogenic disorders, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin-induced platelet aggregation or conditions associated with prostaglandin endoperoxide synthase-2 in a patient, said method comprising administering to said patient a composition according to claim 49.

51. (Added) The method according to claim 50, wherein said method is used to treat an inflammatory disease

selected from acute pancreatitis, chronic pancreatitis, asthma, allergies, or adult respiratory distress syndrome.

52. (Added) The method according to claim 50, wherein said method is used to treat an autoimmune disease selected from glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, or graft vs. host disease.

53. (Added) The method according to claim 50, wherein said method is used to treat a destructive bone disorder selected from osteoarthritis, osteoporosis or multiple myeloma-related bone disorder.

54. (Added) The method according to claim 50, wherein said method is used to treat a proliferative disease selected from acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, or multiple myeloma.

55. (Added) The method according to claim 50, wherein said method is used to treat an infectious disease selected from sepsis, septic shock, or Shigellosis.

56. (Added) The method according to claim 50, wherein said method is used to treat a viral disease selected from acute hepatitis infection, HIV infection or CMV retinitis.

57. (Added) The method according to claim 50, wherein said method is used to treat a neurodegenerative

disease selected from Alzheimer's disease, Parkinson's disease, cerebral ischemia or neurodegenerative disease caused by traumatic injury.

58. (Added) The method according to claim 50, wherein said method is used to treat ischemia/reperfusion in stroke or myocardial ischemia, renal ischemia, heart attacks, organ hypoxia or thrombin-induced platelet aggregation.

C6 59. (Added) The method according to claim 50, wherein said method is used to treat a condition associated with prostaglandin endoperoxide synthase-2 selected from edema, fever, analgesia or pain.

60. (Added) The method according to claim 59, wherein said pain is selected from neuromuscular pain, headache, cancer pain, dental pain or arthritis pain.

61. (Added) The method according to claim 50, wherein said method is used to treat an angiogenic disorder selected from solid tumors, ocular neovascularization, or infantile haemangiomas.

17
62. (Added) A pharmaceutical composition 13 comprising an amount of a compound according to claim 46 effective to inhibit p38, and a pharmaceutically acceptable carrier.

63. (Added) A method of treating inflammatory diseases, autoimmune diseases, viral diseases, destructive bone disorders, proliferative disorders, infectious diseases, neurodegenerative diseases, reperfusion/ischemia in stroke, myocardial ischemia, renal ischemia, heart attacks, angiogenic disorders, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin-induced platelet

128²⁵

E4
cont

aggregation or conditions associated with prostaglandin endoperoxide synthase-2 in a patient, said method comprising administering to said patient a composition according to claim 62.

18

64. (Added) A pharmaceutical composition 14 comprising an amount of a compound according to claim 47 effective to inhibit p38, and a pharmaceutically acceptable carrier.

C6
end
E5

65. (Added) A method of treating inflammatory diseases, autoimmune diseases, viral diseases, destructive bone disorders, proliferative disorders, infectious diseases, neurodegenerative diseases, reperfusion/ischemia in stroke, myocardial ischemia, renal ischemia, heart attacks, angiogenic disorders, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin-induced platelet aggregation or conditions associated with prostaglandin endoperoxide synthase-2 in a patient, said method comprising administering to said patient a composition according to claim 64.

19

66. (Added) A pharmaceutical composition 15 comprising an amount of a compound according to claim 48 effective to inhibit p38, and a pharmaceutically acceptable carrier.

67. (Added) A method of treating inflammatory diseases, autoimmune diseases, viral diseases, destructive bone disorders, proliferative disorders, infectious diseases, neurodegenerative diseases, reperfusion/ischemia in stroke, myocardial ischemia, renal ischemia, heart attacks, angiogenic disorders, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin-induced platelet aggregation or conditions associated with prostaglandin endoperoxide synthase-2 in a patient, said method comprising

26
129

C